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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  SEP 09  ACD predicted properties enhanced in REGISTRY/ZREGISTRY
 NEWS  4  OCT 03  MATHDI removed from STN
 NEWS  5  OCT 04  CA/CAplus-Canadian Intellectual Property Office (CIPO) added
                  to core patent offices
 NEWS  6  OCT 13  New CAS Information Use Policies Effective October 17, 2005
 NEWS  7  OCT 17  STN(R) AnaVist(TM), Version 1.01, allows the export/download
                  of CAplus documents for use in third-party analysis and
                  visualization tools
 NEWS  8  OCT 27  Free KWIC format extended in full-text databases
 NEWS  9  OCT 27  DIOGENES content streamlined
 NEWS 10  OCT 27  EPFULL enhanced with additional content
 NEWS 11  NOV 14  CA/CAplus - Expanded coverage of German academic research
 NEWS 12  NOV 30  REGISTRY/ZREGISTRY on STN(R) enhanced with experimental
                  spectral property data
 NEWS 13  DEC 05  CASREACT(R) - Over 10 million reactions available

 NEWS EXPRESS  DECEMBER 02 CURRENT VERSION FOR WINDOWS IS V8.01,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
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FILE 'HOME' ENTERED AT 09:22:46 ON 14 DEC 2005

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'REGISTRY' ENTERED AT 09:22:55 ON 14 DEC 2005
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STRUCTURE FILE UPDATES: 13 DEC 2005 HIGHEST RN 869843-02-7
DICTIONARY FILE UPDATES: 13 DEC 2005 HIGHEST RN 869843-02-7

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*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
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for details.

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predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

```
=> E "SULINDAC"/CN 25
E1            1      SULIKOL K/CN
E2            1      SULIN/CN
E3            1 --> SULINDAC/CN
E4            1      SULINDAC B Ω-N-METHYL-L-ARGININE SALT/CN
E5            1      SULINDAC B Ω-N-NITRO-L-ARGININE METHYL ESTER SALT/CN
E6            1      SULINDAC B Ω-N-NITRO-L-ARGININE SALT/CN
E7            1      SULINDAC ETHYL ESTER/CN
E8            1      SULINDAC SODIUM/CN
E9            1      SULINDAC SULFIDE/CN
E10           1      SULINDAC SULFONE/CN
E11           1      SULINDAC SULFOXIDE/CN
E12           1      SULINDAC-QUINOLINE/CN
E13           1      SULINEX/CN
E14           1      SULINOL/CN
E15           1      SULIODOVIZOL/CN
E16           1      SULISATIN/CN
E17           1      SULISATIN DISODIUM SALT/CN
E18           1      SULISATIN SODIUM/CN
E19           1      SULISATINE SODIUM/CN
E20           1      SULISOBENZONE/CN
E21           1      SULJEX/CN
E22           1      SULKA/CN
E23           1      SULKA K BOLUSES/CN
E24           1      SULKA N/CN
E25           1      SULKOR/CN

=> S E3
L1            1 SULINDAC/CN
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=> file caplus
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         5.03       5.24

FILE 'CAPLUS' ENTERED AT 09:23:34 ON 14 DEC 2005
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FILE COVERS 1907 - 14 Dec 2005  VOL 143 ISS 25
FILE LAST UPDATED: 13 Dec 2005  (20051213/ED)

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=> s l1
L2        1426 L1

=> s gastrointestingal or esophag? or gastic? or intestin? or colorect?
             2 GASTROINTESTINGAL
         15568 ESOPHAG?
             4 GASTIC?
        239459 INTESTIN?
         18675 COLORECT?
L3      254068 GASTROINTESTINGAL OR ESOPHAG? OR GASTIC? OR INTESTIN? OR COLOREC
               T?

=> s cancer? or tumor? or neoplas? or polyp?
        277857 CANCER?
        411659 TUMOR?
        431921 NEOPLAS?
        438716 POLYP?
L4     1099978 CANCER? OR TUMOR? OR NEOPLAS? OR POLYP?

=> s l4 and l3
L5       65506 L4 AND L3

=> s l5 and l2
L6         234 L5 AND L2

=> s oral?
L7      243958 ORAL?

=> s l7 and l6
L8          30 L7 AND L6

=> s l2 (l) l4
L9         186 L2 (L) L4

=> s l9 and l3
```

```
L10        121 L9 AND L3

=> s l10 and l7
L11         14 L10 AND L7

=> s l14 not py>2002
L14 NOT FOUND
The L-number entered could not be found.  To see the definition
of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

=> s l11 not py>2002
       3346380 PY>2002
L12          9 L11 NOT PY>2002

=> d ibib 1-4

L12  ANSWER 1 OF 9  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2002:723268  CAPLUS
DOCUMENT NUMBER:          138:13001
TITLE:                    A mouse model of human oral-
                          esophageal cancer
AUTHOR(S):                Opitz, Oliver G.; Harada, Hideki; Suliman, Yasir;
                          Rhoades, Ben; Sharpless, Norman E.; Kent, Ralph;
                          Kopelovich, Levy; Nakagawa, Hiroshi; Rustgi, Anil K.
CORPORATE SOURCE:         Division of Gastroenterology, University of
                          Pennsylvania, Philadelphia, PA, 19104-2144, USA
SOURCE:                   Journal of Clinical Investigation (2002), 110(6),
                          761-769
                          CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER:                American Society for Clinical Investigation
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          44    THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12  ANSWER 2 OF 9  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2002:259707  CAPLUS
DOCUMENT NUMBER:          136:379639
TITLE:                    Primary chemoprevention of familial adenomatous
                          polyposis with sulindac
AUTHOR(S):                Giardiello, Francis M.; Yang, Vincent W.; Hylind,
                          Linda M.; Krush, Anne J.; Petersen, Gloria M.;
                          Trimbath, Jill D.; Piantadosi, Steven; Garrett,
                          Elizabeth; Geiman, Deborah E.; Hubbard, Walter;
                          Offerhaus, Johan A.; Hamilton, Stanley R.
CORPORATE SOURCE:         Dep. Med., Johns Hopkins Univ. Sch. Med., Baltimore,
                          MD, USA
SOURCE:                   New England Journal of Medicine (2002), 346(14),
                          1054-1059
                          CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER:                Massachusetts Medical Society
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          23    THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12  ANSWER 3 OF 9  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2001:564792  CAPLUS
DOCUMENT NUMBER:          135:127230
TITLE:                    Method for inhibiting a tumor
INVENTOR(S):              Nair, Muraleedharan G.; Bourquin, Leslie D.; Seeram,
                          Navindra P.; Kang, Soo-Young
PATENT ASSIGNEE(S):       Michigan State University, USA
SOURCE:                   PCT Int. Appl., 27 pp.
                          CODEN: PIXXD2
```

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001054516	A1	20010802	WO 2001-US1196	20010112
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2398389	AA	20010802	CA 2001-2398389	20010112
PRIORITY APPLN. INFO.:			US 2000-494077 A	20000128
			WO 2001-US1196 W	20010112

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:476884 CAPLUS
DOCUMENT NUMBER: 135:282815
TITLE: Sulindac in familial adenomatous polyposis: Evaluation by nuclear morphometry
AUTHOR(S): Fernandez-Lopez, F.; Conde-Freire, R.; Cadarso-Suarez, C.; Garcia-Iglesias, J.; Puente-Dominguez, J. L.; Potel-Lesquereux, J.
CORPORATE SOURCE: General Surgery Department, Hospital Clinico Universitario, Santiago de Compostela, Spain
SOURCE: European Journal of Surgery (2001), 167(5), 375-381
CODEN: EUJSEH; ISSN: 1102-4151
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib 5-9

L12 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:260877 CAPLUS
DOCUMENT NUMBER: 133:217169
TITLE: Sulindac and acetylsalicylic acid (ASA) - clinical relevance in familial adenomatous polyposis
AUTHOR(S): Winde, G.
CORPORATE SOURCE: Klinik und Poliklinik fur Allgemeine Chirurgie der WWU, Munster, D-48129, Germany
SOURCE: Falk Symposium (1999), 109(Colorectal Cancer), 235-255
CODEN: FASYDI; ISSN: 0161-5580
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 91 THERE ARE 91 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:147314 CAPLUS
DOCUMENT NUMBER: 132:273995
TITLE: Inhibition of rat colon tumors by sulindac and sulindac sulfone is independent of K-ras (codon 12)

mutation
AUTHOR(S): De Jong, Tanya A.; Skinner, Stewart A.; Malcontenti-Wilson, Cathy; Vogiagis, Daphne; Bailey, Michael; Van Driel, Ian R.; O'Brien, Paul E.
CORPORATE SOURCE: Department of Surgery, Monash University Medical School, Melbourne, 3181, Australia
SOURCE: American Journal of Physiology (2000), 278(2, Pt. 1), G266-G272
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:18902 CAPLUS
DOCUMENT NUMBER: 132:44655
TITLE: Rectal epithelial apoptosis in familial adenomatous polyposis patients treated with sulindac
AUTHOR(S): Keller, J. J.; Offerhaus, G. J. A.; Polak, M.; Goodman, S. N.; Zahurak, M. L.; Hylind, L. M.; Hamilton, S. R.; Giardiello, F. M.
CORPORATE SOURCE: Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Gut (1999), 45(6), 822-828
CODEN: GUTTAK; ISSN: 0017-5749
PUBLISHER: BMJ Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:277228 CAPLUS
DOCUMENT NUMBER: 124:331957
TITLE: Sulindac induced regression of colorectal adenomas in familial adenomatous polyposis: Evaluation of predictive factors
AUTHOR(S): Giardiello, F. M.; Offerhaus, J. A.; Tersmette, A. C.; Hylind, L. M.; Krush, A. J.; Brensinger, J. D.; Booker, S. V.; Hamilton, S. R.
CORPORATE SOURCE: School Medicine, Johns Hopkins University, Baltimore, MD, 21287, USA
SOURCE: Gut (1996), 38(4), 578-581
CODEN: GUTTAK; ISSN: 0017-5749
PUBLISHER: BMJ Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

L12 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:529697 CAPLUS
DOCUMENT NUMBER: 115:129697
TITLE: Lung tumorigenicity of NNK given orally to A/J mice: its application to chemopreventive efficacy studies
AUTHOR(S): Castonguay, Andre; Pepin, Pierrot; Stoner, Gary D.
CORPORATE SOURCE: Sch. Pharm., Laval Univ., Quebec, QC, G1K 7P4, Can.
SOURCE: Experimental Lung Research (1991), 17(2), 485-99
CODEN: EXLRDA; ISSN: 0190-2148
DOCUMENT TYPE: Journal
LANGUAGE: English

=> d abs 9

L12 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
AB The ability of five chemopreventive agents to inhibit 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung tumors in A/J mice was determined The carcinogen was administered in the drinking water during 7 wk (at doses of 9.2 to 3.1 mg/mouse). Three chemopreventive agents: (dose, g/kg diet) ellagic acid (4.0), 2(3)-BHA (5.0), and sulindac (0.13) inhibited the multiplicity of lung adenomas by 52, 88, and 52%, resp., when compared to NNK controls. β-Carotene + retinol (2.14 + 0.009), in combination, and selenium (0.0022) were ineffective. NNK was absorbed more rapidly from the duodenum than from the stomach and was metabolized in both tissues. The activation of NNK by α-carbon hydroxylation and its deactivation by pyridine N-oxidation was more extensive in the duodenum than in the stomach. Carbonyl reduction of NNK was 10 times higher in the duodenum. Liver microsomes were more active than lung microsomes in the α-carbon hydroxylation of NNK, suggesting that some liver isoenzymes of cytochrome P 450 have a high affinity for NNK. Pyridine N-oxidation was five times more extensive in lung microsomes than in liver microsomes. Collectively, these results demonstrate that NNK given orally to A/J mice provides a suitable model from which to assess the relative activity and mechanisms of action of chemopreventive agents in pulmonary carcinogenesis.

=> d kwic 9

L12 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
TI Lung tumorigenicity of NNK given orally to A/J mice: its application to chemopreventive efficacy studies
AB . . . . N-oxidation was five times more extensive in lung microsomes than in liver microsomes. Collectively, these results demonstrate that NNK given orally to A/J mice provides a suitable model from which to assess the relative activity and mechanisms of action of chemopreventive. . .
IT Intestine, metabolism
(duodenum, (methylnitrosamino)(pyridyl)butanone metabolism by, chemopreventive agents agents against lung neoplasm effect on)
IT 68-26-8, Retinol 476-66-4, Ellagic acid 7235-40-7, β-Carotene 14124-67-5, Selenite 25013-16-5 38194-50-2, Sulindac
RL: BIOL (Biological study)
((methylnitrosamino)(pyridyl)butanone-induced lung neoplasm response to)

=> d ibib abs keic 8
'KEIC' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'

The following are valid formats:

ABS --------- GI and AB
ALL --------- BIB, AB, IND, RE
APPS -------- AI, PRAI
BIB --------- AN, plus Bibliographic Data and PI table (default)
CAN --------- List of CA abstract numbers without answer numbers
CBIB -------- AN, plus Compressed Bibliographic Data
DALL -------- ALL, delimited (end of each field identified)
DMAX -------- MAX, delimited for post-processing
FAM --------- AN, PI and PRAI in table, plus Patent Family data
FBIB -------- AN, BIB, plus Patent FAM
IND --------- Indexing data
IPC --------- International Patent Classifications
MAX --------- ALL, plus Patent FAM, RE
PATS -------- PI, SO
SAM --------- CC, SX, TI, ST, IT
SCAN -------- CC, SX, TI, ST, IT (random display, no answer numbers; SCAN must be entered on the same line as the DISPLAY,

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            e.g., D SCAN or DISPLAY SCAN)
STD --------- BIB, IPC, and NCL

IABS -------- ABS, indented with text labels
IALL -------- ALL, indented with text labels
IBIB -------- BIB, indented with text labels
IMAX -------- MAX, indented with text labels
ISTD -------- STD, indented with text labels

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

HIT --------- Fields containing hit terms
HITIND ------ IC, ICA, ICI, NCL, CC and index field (ST and IT)
              containing hit terms
HITRN ------- HIT RN and its text modification
HITSTR ------ HIT RN, its text modification, its CA index name, and
              its structure diagram
HITSEQ ------ HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and
              its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
KWIC -------- Hit term plus 20 words on either side
OCC --------- Number of occurrence of hit term and field in which it occurs

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an arrow prompt (=>).  Examples of formats include: TI; TI,AU; BIB,ST;
TI,IND; TI,SO.  You may specify the format fields in any order and the
information will be displayed in the same order as the format
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FHITSTR, HITSEQ, FHITSEQ, KWIC, and OCC) may be used with DISPLAY ACC
to view a specified Accession Number.
ENTER DISPLAY FORMAT (BIB):end

=> d ibib abs kwic 8

L12  ANSWER 8 OF 9  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         1996:277228  CAPLUS
DOCUMENT NUMBER:          124:331957
TITLE:                    Sulindac induced regression of colorectal
                          adenomas in familial adenomatous polyposis: Evaluation
                          of predictive factors
AUTHOR(S):                Giardiello, F. M.; Offerhaus, J. A.; Tersmette, A. C.;
                          Hylind, L. M.; Krush, A. J.; Brensinger, J. D.;
                          Booker, S. V.; Hamilton, S. R.
CORPORATE SOURCE:         School Medicine, Johns Hopkins University, Baltimore,
                          MD, 21287, USA
SOURCE:                   Gut (1996), 38(4), 578-581
                          CODEN: GUTTAK; ISSN: 0017-5749
PUBLISHER:                BMJ Publishing Group
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB    Background-Sulindac, a non-steroidal anti-inflammatory drug, causes
      regression of colorectal adenomas in patients with familial
      adenomatous polyposis (FAP) but the response is variable.  Specific clin.
      factors predictive of sulindac induced regression have not been studied.
      Methods-22 patients with FAP were given sulindac 150 mg orally
```

twice a day. Polyp number and size were determined before treatment and at three months. The relation of nine clin. factors to polyp regression (per cent of baseline polyp number after treatment) was evaluated by univariate and multivariate anal. Results-After three months of sulindac, polyp number had decreased to 45 per cent of baseline and polyp size to 50 per cent of baseline (p<0.001 and p<0.01, resp.). Univariate anal. showed greater polyp regression in older patients (p=0.004), those with previous colectomy and ileorectal anastomosis (p=0.001), and patients without identifiable mutation of the APC gene responsible for FAP (p=0.05). With multivariate regression anal., response to sulindac treatment was associated with previous subtotal colectomy. Conclusions-Sulindac treatment seems effective in producing regression of colorectal adenomas of FAP patients with previous subtotal colectomy regardless of baseline polyp number and size. Changed sulindac metabolism, reduced area of the target mucosa, or changed epithelial characteristics after ileorectal anastomosis may explain these findings.

TI Sulindac induced regression of colorectal adenomas in familial adenomatous polyposis: Evaluation of predictive factors

AB Background-Sulindac, a non-steroidal anti-inflammatory drug, causes regression of colorectal adenomas in patients with familial adenomatous polyposis (FAP) but the response is variable. Specific clin. factors predictive of sulindac induced regression have not been studied. Methods-22 patients with FAP were given sulindac 150 mg orally twice a day. Polyp number and size were determined before treatment and at three months. The relation of nine clin. factors to polyp regression (per cent of baseline polyp number after treatment) was evaluated by univariate and multivariate anal. Results-After three months of sulindac, polyp number had decreased to 45 per cent of baseline and polyp size to 50 per cent of baseline (p<0.001 and p<0.01, resp.). Univariate anal. showed greater polyp regression in older patients (p=0.004), those with previous colectomy and ileorectal anastomosis (p=0.001), and patients without identifiable mutation of the APC gene responsible for FAP (p=0.05). With multivariate regression anal., response to sulindac treatment was associated with previous subtotal colectomy. Conclusions-Sulindac treatment seems effective in producing regression of colorectal adenomas of FAP patients with previous subtotal colectomy regardless of baseline polyp number and size. Changed sulindac metabolism, reduced area of the target mucosa, or changed epithelial characteristics after ileorectal anastomosis may explain these findings.

ST sulindac colorectal adenomas adenomatous polyposis

IT Neoplasm inhibitors
(large intestine, sulindac induced regression of colorectal adenomas in familial adenomatous polyposis in humans)

IT Intestine, neoplasm
(large, inhibitors, sulindac induced regression of colorectal adenomas in familial adenomatous polyposis in humans)

IT 38194-50-2, Sulindac
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sulindac induced regression of colorectal adenomas in familial adenomatous polyposis in humans)

=> d ibib abs kwic 2

L12 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:259707 CAPLUS
DOCUMENT NUMBER: 136:379639
TITLE: Primary chemoprevention of familial adenomatous polyposis with sulindac
AUTHOR(S): Giardiello, Francis M.; Yang, Vincent W.; Hylind,

Linda M.; Krush, Anne J.; Petersen, Gloria M.; Trimbath, Jill D.; Piantadosi, Steven; Garrett, Elizabeth; Geiman, Deborah E.; Hubbard, Walter; Offerhaus, Johan A.; Hamilton, Stanley R.
CORPORATE SOURCE: Dep. Med., Johns Hopkins Univ. Sch. Med., Baltimore, MD, USA
SOURCE: New England Journal of Medicine (2002), 346(14), 1054-1059
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: Familial adenomatous polyposis is caused by a germ-line mutation in the adenomatous polyposis coli gene and is characterized by the development of hundreds of colorectal adenomas and, eventually, colorectal cancer. Nonsteroidal antiinflammatory drugs can cause regression of adenomas, but whether they can prevent adenomas is unknown. Methods: The authors conducted a randomized, double-blind, placebo-controlled study of 41 young subjects (age range, 8 to 25 yr) who were genotypically affected with familial adenomatous polyposis but phenotypically unaffected. The subjects received either 75 or 150 mg of sulindac orally twice a day or identical-appearing placebo tablets for 48 mo. The number and size of new adenomas and side effects of therapy were evaluated every four months for four years, and the levels of five major prostaglandins were serially measured in biopsy specimens of normal-appearing colorectal mucosa. Results: After four years of treatment, the average rate of compliance exceeded 76 % in the sulindac group, and mucosal prostaglandin levels were lower in this group than in the placebo group. During the course of the study, adenomas developed in 9 of 21 subjects (43 %) in the sulindac group and 11 of 20 subjects in the placebo group (55 %) (P = 0.54). There were no significant differences in the mean number (P = 0.69) or size (P = 0.17) of polyps between the groups. Sulindac did not slow the development of adenomas, according to an evaluation involving linear longitudinal methods. Conclusions: Standard doses of sulindac did not prevent the development of adenomas in subjects with familial adenomatous polyposis.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Background: Familial adenomatous polyposis is caused by a germ-line mutation in the adenomatous polyposis coli gene and is characterized by the development of hundreds of colorectal adenomas and, eventually, colorectal cancer. Nonsteroidal antiinflammatory drugs can cause regression of adenomas, but whether they can prevent adenomas is unknown. Methods: The authors conducted a randomized, double-blind, placebo-controlled study of 41 young subjects (age range, 8 to 25 yr) who were genotypically affected with familial adenomatous polyposis but phenotypically unaffected. The subjects received either 75 or 150 mg of sulindac orally twice a day or identical-appearing placebo tablets for 48 mo. The number and size of new adenomas and side effects of therapy were evaluated every four months for four years, and the levels of five major prostaglandins were serially measured in biopsy specimens of normal-appearing colorectal mucosa. Results: After four years of treatment, the average rate of compliance exceeded 76 % in the sulindac group, and mucosal prostaglandin levels were lower in this group than in the placebo group. During the course of the study, adenomas developed in 9 of 21 subjects (43 %) in the sulindac group and 11 of 20 subjects in the placebo group (55 %) (P = 0.54). There were no significant differences in the mean number (P = 0.69) or size (P = 0.17) of polyps between the groups. Sulindac did not slow the development of adenomas, according to an evaluation involving linear longitudinal methods. Conclusions: Standard doses of sulindac did not prevent the development of adenomas in subjects with familial adenomatous polyposis.
IT Prostaglandins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(colorectal mucosa prostaglandin levels as measure of

```
        sulindac local effect in humans with familial adenomatous polyposis)
IT   Antitumor agents
        (colorectal, adenoma; primary chemoprevention of familial
        adenomatous polyposis with sulindac in humans)
IT   Intestine, neoplasm
        (colorectal, inhibitors, adenoma; primary chemoprevention of
        familial adenomatous polyposis with sulindac in humans)
IT   Intestine, neoplasm
        (familial polyposis; primary chemoprevention of familial adenomatous
        polyposis with sulindac in humans)
IT   Intestine
        (large, mucosa; colorectal mucosa prostaglandin levels as
        measure of sulindac local effect in humans with familial adenomatous
        polyposis)
IT   363-24-6, Prostaglandin E2   551-11-1, Prostaglandin F2α
     13367-85-6, Prostaglandin B2   41598-07-6, Prostaglandin D2   58962-34-8,
     6-keto-Prostaglandin F1α
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (colorectal mucosa prostaglandin levels as measure of
        sulindac local effect in humans with familial adenomatous polyposis)
IT   38194-50-2, Sulindac
     RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological
     activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (primary chemoprevention of familial adenomatous polyposis
        with sulindac in humans)


=> d his

     (FILE 'HOME' ENTERED AT 09:22:46 ON 14 DEC 2005)

     FILE 'REGISTRY' ENTERED AT 09:22:55 ON 14 DEC 2005
                E "SULINDAC"/CN 25
L1             1 S E3

     FILE 'CAPLUS' ENTERED AT 09:23:34 ON 14 DEC 2005
L2          1426 S L1
L3        254068 S GASTROINTESTINGAL OR ESOPHAG? OR GASTIC? OR INTESTIN? OR COLO
L4       1099978 S CANCER? OR TUMOR? OR NEOPLAS? OR POLYP?
L5         65506 S L4 AND L3
L6           234 S L5 AND L2
L7        243958 S ORAL?
L8            30 S L7 AND L6
L9           186 S L2 (L) L4
L10          121 S L9 AND L3
L11           14 S L10 AND L7
L12            9 S L11 NOT PY>2002

=> s lipsom? or microspher? or encapsulat? or polymer?
             74 LIPSOM?
          27180 MICROSPHER?
          55572 ENCAPSULAT?
        1820552 POLYMER?
          84067 POLYMD
          84067 POLYMD
                  (POLYMD)
          31147 POLYMG
         326031 POLYMN
           8505 POLYMNS
         327118 POLYMN
                  (POLYMN OR POLYMNS)
        1885881 POLYMER?
                  (POLYMER? OR POLYMD OR POLYMG OR POLYMN)
L13     1945587 LIPSOM? OR MICROSPHER? OR ENCAPSULAT? OR POLYMER?
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=> s l13 and l12
L14             0 L13 AND L12

=> s l4 and l2
L15           443 L4 AND L2

=> s l9 and l13
L16            12 L9 AND L13

=> s l16 not py>2002
       3346380 PY>2002
L17             3 L16 NOT PY>2002

=> d ibib 1-3

L17  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2001:430708  CAPLUS
DOCUMENT NUMBER:          135:236055
TITLE:                    Rat colorectal tumors treated with a range of
                          nonsteroidal anti-inflammatory drugs show altered
                          cyclooxygenase-2 and cyclooxygenase-1 splice variant
                          mRNA expression levels
AUTHOR(S):                Vogiagis, Daphne; Brown, Wendy; Glare, Eric M.;
                          O'Brien, Paul E.
CORPORATE SOURCE:         Department of Surgery, Monash University Medical
                          School, Alfred Hospital, Prahran, 3181, Australia
SOURCE:                   Carcinogenesis (2001), 22(6), 869-874
                          CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER:                Oxford University Press
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          49    THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17  ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         1998:457250  CAPLUS
DOCUMENT NUMBER:          129:76490
TITLE:                    Method for treating a tumor with a chemotherapeutic
                          agent and nonemulsified ultrapurified
                          polymerized hemoglobin solution
INVENTOR(S):              Teicher, Beverly A.; Rausch, Carl W.; Hopkins, Robert
                          E., II
PATENT ASSIGNEE(S):       Dana-Farber Cancer Institute, USA; Biopure Corp.
SOURCE:                   U.S., 16 pp., Cont.-in-part of U. S. Ser. No. 94,501.
                          CODEN: USXXAM
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   3
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    --------------------     --------
     US 5776898            A     19980707    US 1995-477110           19950607
     US 5679638            A     19971021    US 1993-94501            19930720
PRIORITY APPLN. INFO.:                       US 1991-699769       A2  19910514
                                             US 1993-94501        A2  19930720
REFERENCE COUNT:          59    THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17  ANSWER 3 OF 3  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         1997:689536  CAPLUS
DOCUMENT NUMBER:          127:326520
TITLE:                    Method for treating a tumor with a chemotherapeutic
                          agent
INVENTOR(S):              Teicher, Beverly A.; Rausch, Carl W.; Hopkins, Robert
```

E., II
PATENT ASSIGNEE(S): Biopure Corporation, USA; Dana Farber Cancer Institute
SOURCE: U.S., 12 pp., Cont.-in-part of U.S. Ser. No. 699,769,abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5679638	A	19971021	US 1993-94501	19930720
US 5776898	A	19980707	US 1995-477110	19950607
PRIORITY APPLN. INFO.:			US 1991-699769	B2 19910514
			US 1993-94501	A2 19930720

=> d ibib abs kwic 1

L17 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:430708 CAPLUS
DOCUMENT NUMBER: 135:236055
TITLE: Rat colorectal tumors treated with a range of nonsteroidal anti-inflammatory drugs show altered cyclooxygenase-2 and cyclooxygenase-1 splice variant mRNA expression levels
AUTHOR(S): Vogiagis, Daphne; Brown, Wendy; Glare, Eric M.; O'Brien, Paul E.
CORPORATE SOURCE: Department of Surgery, Monash University Medical School, Alfred Hospital, Prahran, 3181, Australia
SOURCE: Carcinogenesis (2001), 22(6), 869-874
CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce tumor mass by increasing tumor cell apoptosis and decreasing cell proliferation. The classically recognized targets for NSAID action are the two isoforms of the cyclooxygenase (COX) gene, which is responsible for prostaglandin production In the rat, the COX-1 gene expresses an alternatively spliced mRNA COX-1 splice variant (SV) which may, at best, code for a truncated COX-1 protein. Previously, it was reported that COX-1SV mRNA is differentially expressed in the ageing stomach. In this study, carcinogen-treated rats were treated for 23 wk with the NSAIDs celecoxib, sulindac or sulindac sulfone, while untreated rats received vehicle alone. The nos. and vols. of tumor per animal were recorded and histol. was performed. The competitive polymerase chain reaction, was used to determine whether COX gene expression was altered in colorectal tumors and in regions of adjacent and distant macroscopically normal intestine, from vehicle- or NSAID-treated rats. In addition, COX-1 and COX-2 were immunolocalized in the same tumor and normal colonic tissue. Tumors from animals treated with vehicle or celecoxib expressed elevated levels of COX-2 mRNA in comparison with the adjacent normal mucosa. In contrast, tumors from sulindac- and sulindac sulfone-treated rats expressed less COX-2 mRNA than tumors from vehicle-treated rats. The expression of COX-1 mRNA remained unchanged in all tissues examined However, COX-1SV mRNA contents were elevated in colorectal tumors and reduced after NSAID treatment to the values in normal colonic mucosa. The results indicate that the antineoplastic actions of NSAIDs may be attributed to COX-dependent and/or COX-independent mechanisms of action. The presence and differential expression of COX-1SV mRNA was also demonstrated in colon tumors. COX-1SV mRNA represents 2% of the total COX-1 mRNA expressed and its role in colon cancer remains to be established.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce tumor mass by increasing tumor cell apoptosis and decreasing cell proliferation. The classically recognized targets for NSAID action are the two isoforms of the cyclooxygenase (COX) gene, which is responsible for prostaglandin production In the rat, the COX-1 gene expresses an alternatively spliced mRNA COX-1 splice variant (SV) which may, at best, code for a truncated COX-1 protein. Previously, it was reported that COX-1SV mRNA is differentially expressed in the ageing stomach. In this study, carcinogen-treated rats were treated for 23 wk with the NSAIDs celecoxib, sulindac or sulindac sulfone, while untreated rats received vehicle alone. The nos. and vols. of tumor per animal were recorded and histol. was performed. The competitive polymerase chain reaction, was used to determine whether COX gene expression was altered in colorectal tumors and in regions of adjacent and distant macroscopically normal intestine, from vehicle- or NSAID-treated rats. In addition, COX-1 and COX-2 were immunolocalized in the same tumor and normal colonic tissue. Tumors from animals treated with vehicle or celecoxib expressed elevated levels of COX-2 mRNA in comparison with the adjacent normal mucosa. In contrast, tumors from sulindac- and sulindac sulfone-treated rats expressed less COX-2 mRNA than tumors from vehicle-treated rats. The expression of COX-1 mRNA remained unchanged in all tissues examined However, COX-1SV mRNA contents were elevated in colorectal tumors and reduced after NSAID treatment to the values in normal colonic mucosa. The results indicate that the antineoplastic actions of NSAIDs may be attributed to COX-dependent and/or COX-independent mechanisms of action. The presence and differential expression of COX-1SV mRNA was also demonstrated in colon tumors. COX-1SV mRNA represents 2% of the total COX-1 mRNA expressed and its role in colon cancer remains to be established.

IT 38194-50-2, Sulindac 59973-80-7, Sulindac sulfone 169590-42-5, Celecoxib
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(colorectal tumors treated with nonsteroidal anti-inflammatory drugs show altered cyclooxygenase-2 and cyclooxygenase-1 splice variant mRNA expression)

=> file medline

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	64.77	70.01

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.65	-3.65

FILE 'MEDLINE' ENTERED AT 09:35:28 ON 14 DEC 2005

FILE LAST UPDATED: 8 DEC 2005 (20051208/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 will soon be available. For details on the 2005 reload, enter HELP RLOAD at an arrow promt (=>).
See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the

MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> s SULINDAC/CN
L18         919 SULINDAC/CN

=> s cancer? or tumor? or neoplas? or polyp?
        547932 CANCER?
        758323 TUMOR?
       1455946 NEOPLAS?
        155044 POLYP?
L19    1879233 CANCER? OR TUMOR? OR NEOPLAS? OR POLYP?

=> s gastrointestingal or esophag? or gastic? or intestin? or colorect?
             1 GASTROINTESTINGAL
        101857 ESOPHAG?
            50 GASTIC?
        293936 INTESTIN?
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L20     428581 GASTROINTESTINGAL OR ESOPHAG? OR GASTIC? OR INTESTIN? OR COLOREC
               T?

=> s l19 and l20
L21     125328 L19 AND L20

=> s l21 and l18
L22        175 L21 AND L18

=> s liposom? or microspher? or encapsulat? or polymer?
         30623 LIPOSOM?
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L23     407843 LIPOSOM? OR MICROSPHER? OR ENCAPSULAT? OR POLYMER?

=> s l23 and l22
L24           8 L23 AND L22

=> s l24 not py>2002
       1733376 PY>2002
L25           6 L24 NOT PY>2002

=> d ibib 1-3

L25  ANSWER 1 OF 6     MEDLINE on STN
ACCESSION NUMBER:   2002696841     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12458338
TITLE:              Effects of long-term administration of sulindac on APC mRNA
                    and apoptosis in colons of rats treated with azoxymethane.
AUTHOR:             Kishimoto Y; Yashima K; Morisawa T; Ohishi T; Marumoto A;
                    Sano A; Idobe-Fujii Y; Miura N; Shiota G; Murawaki Y;
                    Hasegawa J
CORPORATE SOURCE:   Division of Pharmacotherapeutics, Department of
                    Pathophysiological and Therapeutic Science, Faculty of
                    Medicine, Tottori University, 86 Nishicho, Yonago 683-8503,
                    Japan.. ykishimo@grape.med.tottori-u.ac.jp
SOURCE:             Journal of cancer research and clinical oncology, (2002
                    Nov) 128 (11) 589-95. Electronic Publication: 2002-10-04.
                    Journal code: 7902060. ISSN: 0171-5216.
PUB. COUNTRY:       Germany: Germany, Federal Republic of
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
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ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20021217
Last Updated on STN: 20030118
Entered Medline: 20030117

L25 ANSWER 2 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2001065648 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11093808
TITLE: Growth-suppressive effect of non-steroidal anti-inflammatory drugs on 11 colon-cancer cell lines and fluorescence differential display of genes whose expression is influenced by sulindac.
AUTHOR: Akashi H; Han H J; Iizaka M; Nakamura Y
CORPORATE SOURCE: Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, University of Tokyo, Tokyo, Japan.
SOURCE: International journal of cancer. Journal international du cancer, (2000 Dec 15) 88 (6) 873-80.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001222

L25 ANSWER 3 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2001064500 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11076880
TITLE: Sulindac and a cyclooxygenase-2 inhibitor, etodolac, increase APC mRNA in the colon of rats treated with azoxymethane.
AUTHOR: Kishimoto Y; Takata N; Jinnai T; Morisawa T; Shiota G; Kawasaki H; Hasegawa J
CORPORATE SOURCE: Department of Clinical Pharmacology, Faculty of Medicine, Tottori University, 86 Nishicho, Yonago 683-8503, Japan.. ykishimo@grape.med.tottori-u.ac.jp
SOURCE: Gut, (2000 Dec) 47 (6) 812-9.
Journal code: 2985108R. ISSN: 0017-5749.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001222

=> d ibib 4-6

L25 ANSWER 4 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2000295032 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10833474
TITLE: Par-4, a proapoptotic gene, is regulated by NSAIDs in human colon carcinoma cells.
AUTHOR: Zhang Z; DuBois R N
CORPORATE SOURCE: Division of Gastroenterology, Department of Medicine and Cell Biology, Vanderbilt University Medical Center, Veterans Affairs Medical Center, Nashville, Tennessee, USA.
CONTRACT NUMBER: DK47297 (NIDDK)
P30 CA68485 (NCI)
PO CA77839 (NCI)

SOURCE: Gastroenterology, (2000 Jun) 118 (6) 1012-7.
Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20021219
Entered Medline: 20000621

L25 ANSWER 5 OF 6 MEDLINE on STN
ACCESSION NUMBER: 1999333404 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10403841
TITLE: Redistribution of activated caspase-3 to the nucleus during butyric acid-induced apoptosis.
AUTHOR: Mandal M; Adam L; Kumar R
CORPORATE SOURCE: Cell Growth Regulation Laboratory, University of Texas M.D. Anderson Cancer Center, Houston, Texas, 77030, USA.
SOURCE: Biochemical and biophysical research communications, (1999 Jul 14) 260 (3) 775-80.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990827
Last Updated on STN: 20020420
Entered Medline: 19990816

L25 ANSWER 6 OF 6 MEDLINE on STN
ACCESSION NUMBER: 96334961 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8707116
TITLE: Sulindac increases the expression of APC mRNA in malignant colonic epithelial cells: an in vitro study.
AUTHOR: Schnitzler M; Dwight T; Robinson B G
CORPORATE SOURCE: Molecular Genetics Unit, Kolling Institute of Medical Research, Royal North Shore Hospital, St Leonards, NSW, Australia.
SOURCE: Gut, (1996 May) 38 (5) 707-13.
Journal code: 2985108R. ISSN: 0017-5749.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960919
Last Updated on STN: 19970203
Entered Medline: 19960910

=> d ibib abs kwic 4

L25 ANSWER 4 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2000295032 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10833474
TITLE: Par-4, a proapoptotic gene, is regulated by NSAIDs in human colon carcinoma cells.
AUTHOR: Zhang Z; DuBois R N
CORPORATE SOURCE: Division of Gastroenterology, Department of Medicine and Cell Biology, Vanderbilt University Medical Center, Veterans Affairs Medical Center, Nashville, Tennessee, USA.
CONTRACT NUMBER: DK47297 (NIDDK)
P30 CA68485 (NCI)

PO CA77839 (NCI)
SOURCE: Gastroenterology, (2000 Jun) 118 (6) 1012-7.
Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20021219
Entered Medline: 20000621

AB BACKGROUND & AIMS: Many reports indicate that nonsteroidal anti-inflammatory drugs (NSAIDs) have antineoplastic effects, but the precise molecular mechanism(s) responsible are unclear. We evaluated the effect of cyclooxygenase (COX) inhibitors (NSAIDs) on human colon carcinoma cells (HCA-7) and identified several genes that are regulated after treatment with NS-398, a selective COX-2 inhibitor. METHODS: Differential display polymerase chain reaction cloning techniques were used to identify genes regulated by treatment with NSAIDs and selective COX-2 inhibitors. RESULTS: A prostate apoptosis response 4 (Par-4) gene was up-regulated after NSAID treatment. Par-4 was first isolated from prostate carcinoma cells undergoing apoptosis, and expression of Par-4 sensitized cancer cells to apoptotic stimuli. Par-4 levels were increased in cells treated with COX inhibitors such as NS-398, nimesulide, SC-58125, and sulindac sulfide. Treatment of HCA-7 cells with these agents also induced apoptotic cell death. CONCLUSIONS: The results suggest that regulation of Par-4 contributes to the proapoptotic effects of high-dose COX inhibitors (NSAIDs) by serving as a downstream mediator leading to initiation of programmed cell death.

AB . . . cells (HCA-7) and identified several genes that are regulated after treatment with NS-398, a selective COX-2 inhibitor. METHODS: Differential display polymerase chain reaction cloning techniques were used to identify genes regulated by treatment with NSAIDs and selective COX-2 inhibitors. RESULTS: A. . . was up-regulated after NSAID treatment. Par-4 was first isolated from prostate carcinoma cells undergoing apoptosis, and expression of Par-4 sensitized cancer cells to apoptotic stimuli. Par-4 levels were increased in cells treated with COX inhibitors such as NS-398, nimesulide, SC-58125, and. . .

CT . . . pharmacology
*Apoptosis: DE, drug effects
Apoptosis: GE, genetics
Blotting, Northern
Blotting, Western
Carrier Proteins: AN, analysis
*Carrier Proteins: GE, genetics
Colonic Neoplasms
Cyclooxygenase Inhibitors: PD, pharmacology
DNA Fragmentation
Gene Expression: DE, drug effects
Gene Expression: PH, physiology
Humans
Intestinal Mucosa: CH, chemistry
*Intestinal Mucosa: CY, cytology
Intestinal Mucosa: EN, enzymology
*Intracellular Signaling Peptides and Proteins
*Nitrobenzenes: PD, pharmacology
Protein Kinase C: ME, metabolism
Pyrazoles: PD, pharmacology
. . . Support, U.S. Gov't, Non-P.H.S.
Research Support, U.S. Gov't, P.H.S.
*Sulfonamides: PD, pharmacology
Sulindac: AA, analogs & derivatives
Sulindac: PD, pharmacology
Tumor Cells, Cultured

RN 123653-11-2 (N-(2-cyclohexyloxy-4-nitrophenyl)methanesulfonamide);

162054-19-5 (1-((4-methylsulfonyl)phenyl)-3-trifluoromethyl-5-(4-fluorophenyl)pyrazole); 32004-67-4 (sulindac sulfide); 38194-50-2 (Sulindac); 51803-78-2 (nimesulide)

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=> d his

     (FILE 'HOME' ENTERED AT 09:22:46 ON 14 DEC 2005)

     FILE 'REGISTRY' ENTERED AT 09:22:55 ON 14 DEC 2005
               E "SULINDAC"/CN 25
L1             1 S E3

     FILE 'CAPLUS' ENTERED AT 09:23:34 ON 14 DEC 2005
L2          1426 S L1
L3        254068 S GASTROINTESTINGAL OR ESOPHAG? OR GASTIC? OR INTESTIN? OR COLO
L4       1099978 S CANCER? OR TUMOR? OR NEOPLAS? OR POLYP?
L5         65506 S L4 AND L3
L6           234 S L5 AND L2
L7        243958 S ORAL?
L8            30 S L7 AND L6
L9           186 S L2 (L) L4
L10          121 S L9 AND L3
L11           14 S L10 AND L7
L12            9 S L11 NOT PY>2002
L13      1945587 S LIPSOM? OR MICROSPHER? OR ENCAPSULAT? OR POLYMER?
L14            0 S L13 AND L12
L15          443 S L4 AND L2
L16           12 S L9 AND L13
L17            3 S L16 NOT PY>2002

     FILE 'MEDLINE' ENTERED AT 09:35:28 ON 14 DEC 2005
L18          919 S SULINDAC/CN
L19      1879233 S CANCER? OR TUMOR? OR NEOPLAS? OR POLYP?
L20       428581 S GASTROINTESTINGAL OR ESOPHAG? OR GASTIC? OR INTESTIN? OR COLO
L21       125328 S L19 AND L20
L22          175 S L21 AND L18
L23       407843 S LIPOSOM? OR MICROSPHER? OR ENCAPSULAT? OR POLYMER?
L24            8 S L23 AND L22
L25            6 S L24 NOT PY>2002

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     3.52      73.53

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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FILE LAST UPDATED: 13 Dec 2005  (20051213/ED)

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=> s liposom? or microspher? or encapsulat? or polymer?
         48683 LIPOSOM?
         27180 MICROSPHER?
         55572 ENCAPSULAT?
       1820552 POLYMER?
         84067 POLYMD
         84067 POLYMD
                 (POLYMD)
         31147 POLYMG
        326031 POLYMN
          8505 POLYMNS
        327118 POLYMN
                 (POLYMN OR POLYMNS)
       1885881 POLYMER?
                 (POLYMER? OR POLYMD OR POLYMG OR POLYMN)
L26    1984458 LIPOSOM? OR MICROSPHER? OR ENCAPSULAT? OR POLYMER?

=> s l9 and l26
L27         15 L9 AND L26

=> s liposom? or microspher? or encapsulat?
         48683 LIPOSOM?
         27180 MICROSPHER?
         55572 ENCAPSULAT?
L28     122087 LIPOSOM? OR MICROSPHER? OR ENCAPSULAT?

=> s l28 and l9
L29         11 L28 AND L9

=> s l29 not py>2002
       3346380 PY>2002
L30          0 L29 NOT PY>2002

=> s l29 not py>2003
       2266400 PY>2003
L31          0 L29 NOT PY>2003

=> d l29 ibib 1-4

L29  ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:591975  CAPLUS
DOCUMENT NUMBER:          143:53482
TITLE:                    Method for inhibiting the growth of gastrointestinal
                          tract tumors
INVENTOR(S):              Egilmez, Nejat K.
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 21 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     US 2005147689         A1    20050707    US 2003-748003          20031230
```

CA 2491338	AA	20050630	CA 2004-2491338	20041223
PRIORITY APPLN. INFO.:			US 2003-748003 A	20031230

L29 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:14227 CAPLUS
DOCUMENT NUMBER: 142:107439
TITLE: Cardiolipin synthesis inhibitor for treatment of cardiovascular disorders, and obesity
INVENTOR(S): Jamil, Haris; Ahmad, Moghis U.; Ahmad, Imran
PATENT ASSIGNEE(S): Neopharm, Inc., USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005000318	A2	20050106	WO 2004-US20104	20040623
WO 2005000318	A3	20050414		
WO 2005000318	B1	20050526		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:			US 2003-480669P	P 20030623

L29 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:877933 CAPLUS
DOCUMENT NUMBER: 141:365149
TITLE: Anti-PSGL-1 antibodies and scFv fragments for diagnosis, prognosis and therapy of cancer, metastasis, autoimmune disease and inflammation
INVENTOR(S): Levanon, Avigdor; Ben-Levy, Rachel; Plaksin, Daniel; Szanton, Esther; Hagai, Yocheved; Mar-Chaim, Hagit Hoch
PATENT ASSIGNEE(S): Israel
SOURCE: U.S. Pat. Appl. Publ., 49 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004208877	A1	20041021	US 2003-611588	20030630
PRIORITY APPLN. INFO.:			US 2002-393491P	P 20020701

L29 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:856929 CAPLUS
DOCUMENT NUMBER: 141:348831
TITLE: Antibodies specific to epitopes involving cell rolling, metastasis and inflammation for treatment of tumor, restenosis, thrombosis, autoimmune disease and inflammation
INVENTOR(S): Lazarovits, Janette; Nimrod, Abraham; Hoch, Mar-Chaim

```
                          Hagit; Levanon, Avigdor
PATENT ASSIGNEE(S):       Israel
SOURCE:                   U.S. Pat. Appl. Publ., 22 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     --------------       ----   --------    --------------------     --------
     US 2004202665         A1    20041014    US 2003-610843           20030630
PRIORITY APPLN. INFO.:                       US 2002-393453P     P    20020701


=> file pctfull
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=> s SULINDAC
L32         2826 SULINDAC

=> s l32/ab
L33            9 (SULINDAC/AB)

=> s cancer? or tumor? or neoplas? or polyp?
           73935 CANCER?
           61948 TUMOR?
           21353 NEOPLAS?
          153344 POLYP?
L34       196562 CANCER? OR TUMOR? OR NEOPLAS? OR POLYP?

=> s l34 and l33
L35            7 L34 AND L33

=> s gastrointestingal or esophag? or gastic? or intestin? or colorect?
               4 GASTROINTESTINGAL
           11126 ESOPHAG?
              83 GASTIC?
           38774 INTESTIN?
            8423 COLORECT?
L36        47131 GASTROINTESTINGAL OR ESOPHAG? OR GASTIC? OR INTESTIN? OR COLOREC
                 T?

=> s gastrointestinal or esophag? or gastic? or intestin? or colorect?
           28847 GASTROINTESTINAL
```

```
            9 GASTROINTESTINALS
        28851 GASTROINTESTINAL
                (GASTROINTESTINAL OR GASTROINTESTINALS)
        11126 ESOPHAG?
           83 GASTIC?
        38774 INTESTIN?
         8423 COLORECT?
L37     59284 GASTROINTESTINAL OR ESOPHAG? OR GASTIC? OR INTESTIN? OR COLORECT
              ?

=> s l37 and l35
L38         7 L37 AND L35

=> s liposom? or microspher? or encapsulat?
        40590 LIPOSOM?
        15203 MICROSPHER?
        61501 ENCAPSULAT?
L39     90511 LIPOSOM? OR MICROSPHER? OR ENCAPSULAT?

=> s l39 and l38
L40         2 L39 AND L38

=> d ibib 1-2

L40    ANSWER 1 OF 2     PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:       2001035956 PCTFULL  ED 20020820
TITLE (ENGLISH):        USE OF NSAIDs FOR THE TREATMENT OF PANCREATIC
                        CANCER
TITLE (FRENCH):         UTILISATION DES AINS DANS LE TRAITEMENT DU
                        CANCER DU PANCREAS
INVENTOR(S):            MARSHALL, Mark, Steven;
                        SWEENEY, Christopher, J.;
                        YIP-SCHNEIDER, Michelle, T.;
                        CROWELL, Pamela, L.
PATENT ASSIGNEE(S):     ADVANCED RESEARCH AND TECHNOLOGY INSTITUTE, INC.;
                        MARSHALL, Mark, Steven;
                        SWEENEY, Christopher, J.;
                        YIP-SCHNEIDER, Michelle, T.;
                        CROWELL, Pamela, L.
DOCUMENT TYPE:          Patent
PATENT INFORMATION:
                        NUMBER              KIND     DATE
                        ---------------------------------
                        WO 2001035956         A1 20010525
DESIGNATED STATES
       W:               AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU
                        CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN
                        IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK
                        MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM
                        TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD
                        SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY
                        DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF
                        CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.:      WO 2000-US31410       A  20001115
PRIORITY INFO.:         US 1999-60/165,543       19991115

L40    ANSWER 2 OF 2     PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:       1999049859 PCTFULL  ED 20020515
TITLE (ENGLISH):        DFMO AND SULINDAC COMBINATION IN CANCER
                        CHEMOPREVENTION
TITLE (FRENCH):         COMBINAISON DE DFMO ET DE SULINDAC DANS LA
                        CHIMIOPREVENTION DU CANCER
INVENTOR(S):            GERNER, Eugene, W.;
                        MEYSKENS, Frank, L., Jr.
PATENT ASSIGNEE(S):     THE ARIZONA BOARD OF REGENTS on behalf of THE
```

UNIVERSITY OF ARIZONA;
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA;
GERNER, Eugene, W.;
MEYSKENS, Frank, L., Jr.

LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9949859	A1	19991007

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 1999-US6693 A 19990326
PRIORITY INFO.: US 1998-60/079,850 19980328

=> d kwic 1

L40 ANSWER 1 OF 2 PCTFULL COPYRIGHT 2005 Univentio on STN
TIEN USE OF NSAIDs FOR THE TREATMENT OF PANCREATIC CANCER
TIFR UTILISATION DES AINS DANS LE TRAITEMENT DU CANCER DU PANCREAS
ABEN The invention provides a method comprising the use of non-steroidal antiinflammatory drugs (NSAIDs), particularly sulindac or its analogs to treat pancreatic cancer.

DETD USE OF NSAIDs FOR THE TREATMENT OF PANCREATIC CANCER
Backgrround of the Invention
Cancer of the pancreas ranks 'ust behind lung cancer , colon cancer, and breast cancer as the most common cause of death by cancer (1). It is more common among men, and men between the ages of 60 and 70 are most at risk.

The cause of pancreatic cancer is unknown.
. . .
which are not fully understood, usually is 1 0 significant. The average loss is about 25 pounds. Jaundice occurs if the cancer blocks the common bile duct. The survival rate with pancreatic cancer is poor.

By the time the malignant tumor is identified, it often has spread (metastasized) to other parts of the body. The median survival is little more than six.
. .

5 Often the tumor cannot be removed by surgery, either because it has invaded vital structures that cannot be removed or because it has spread to distant sites. Chemotherapy and radiation therapy can be used on the tumor, although these treatments often are not beneficial.
. .. .
Easton, PA (18th ed., 1990) at pages 1115
There is a large amount of literature on the effect of NSAIDs on

cancer,
particularly colon cancer. For example, see H. A. Weiss et
al., Scand J.
. .
in vitro, but that
indomethacin, ketoralac and NS-398, did not. Sulindac has been
investigated in
combination therapy for the treatment of colon cancer. See, H.
M. Verheul et al.,
Brit- J. Cance , 79, 114 (1999); F. A. Sinicrope et al., Clin.
Cancer Res-, 2, 37
(1996); and M. Mooghen et al., J. Pathol., LI]6, 394 (1988).

C. P. Duffy et al., Eur. J. Cancer, 34, 1250 (1998), reported
that the
cytotoxicity of certain chemotherapeutic drugs was enhanced when they
were
combined with certain non-steroidal anti-inflammatory agents. The
effects
observed against human lung cancer cells and human leukemia
cells were highly
specific and not predictable; i.e., some combinations of NSAID and agent
were
effective and some. . .
. .
a PCT application (WO98/18490) on October 24,
1997, directed to a combination of a substrate for MRP, which can be an
anti-
cancer drug, and a NSAID that increases the potency of the
anti-cancer drug.

Therefore, a continuing need exists for methods to control
cancers, and to
increase the potency of anti-cancer drugs with relatively
non-toxic agents.

Summ= of the Invention
In one aspect, the present invention provides a therapeutic method to
treat
pancreatic cancer, comprising administering to a mammal
afflicted with
pancreatic cancer an amount of a NSAID, preferably sulindac
((Z) fluoro
methyl-l-[[4-(methylsulfinyl)phenyl] methylene]-IH-Indene acetic acid),
or
an analocr thereof, preferably one that is a COX-2 inhibitor, effective
to inhibit
the viability of pancreatic cancer cells of said mammal. The
present invention
also provides a method of increasing the susceptibility of human
pancreatic
cancer cells to a chemotherapeutic agent comprising contacting
the cells with an
effective sensitizing amount of a NSAID, preferably sulindac, or said
analog
thereof Thus, the invention provides a therapeutic method for the
treatment of a
human or other mammal afflicted with pancreatic cancer,
wherein an effective
amount of an NSAID, preferably sulindac or said analog thereof is
administered
to a subject afflicted with pancreatic cancer and undergoing
treatment with a
5 chemotherapeutic (antineoplastic) agent.

Preferably, sulindac is administered in conjunction with one or more chemotherapeutic agents effective against pancreatic cancer such as gemcitabine or 5-FU.

A method of evaluating the ability of sulindac to sensitize pancreatic cancer cells to a chemotherapeutic agent is also provided. The assay method comprises: (a) isolating a first portion of pancreatic cancer cells ftom a human cancer patient; (b) measuring their viability; (c) administering sulindac, or said analog thereof, to said patient; (d) isolating a second portion of pancreatic cancer cells from said patient; (e) measuring the viability of the second portion of pancreatic cancer cells; and (f) comparing the viability measured in step (e) with the viability measured in step (b); wherein reduced viability in. . . . (b) and (e) are carried out in the presence of the chemotherapeutic agent, as will be the case when the pancreatic cancer cells are derived from the blood of a mammal afflicted with pancreatic cancer.

Thus, a cancer patient about to undergo, or undergoing, treatment for pancreatic cancer can be rapidly evaluated to see if he/she will benefit from concurrent chemotherapy and administration of sulindac or an analog thereof.

. . .

Description of the FiVures

Figure 1. Photocopy of a representative immunoblot of pancreatic adenocarcinomas and matched normal tissue. Lysates were prepared from tumor (T) specimens obtained from six patients, three with matched normal (N) tissue (sample numbers correspond to those listed in Table 1). Lysates. . . expresses neither COX- I or COX

Figure 2. Percent COX-2 expression in patient samples. Values of % COX-2 expression for all tumor samples, shown by solid circles, and non-nal tissue, shown by open circles, from Table I are plotted. Values for mean, median and range are indicated. The % COX-2 expression for the matched pancreatic tumor/normal tissue sets is shown in the inset (n = I 1). Lines are drawn between the corresponding tumor values, shown by solid circles, and non-nal values, shown by the open circles. The difference in COX-2 expression between tumor and non-nal specimens was determined to be statistically significant (P = 0.004).

Figure 3. COX-2 expression in pancreatic tumor cell lines. A) COX-2 expression in human pancreatic cell lines detected by immunoblot analysis. The K-ras mutation status of each of the. . .

Figure 4. Effect of COX inhibitors on the growth of pancreatic tumor

cell lines. The cell lines BxPC-3, shown by the black bars, and PaCa-2, shown
by the hatched bars, were plated in the. . .

Figure 5. Prostaglandin E2 production. A) PGE2 levels in pancreatic tumor cell lines. Following incubation of exponentially growing cells with
15 gM arachidonic acid in serum-free media for one hour, PGE2 levels. .

Figure 6 is a graph depicting the effect of a combination of sulindac and
gemcitabine on the growth of pancreatic tumor cell line BxPC.

Figure 7 is a graph depicting the effect of a combination of sulindac and
gemcitabine on the growth of pancreatic tumor cell line PaCa
Detailed Description of the Invention
Difficulty in achieving early diagnosis as well as the aggressive nature of
pancreatic cancer contribute to the low survival rate of patients with pancreatic cancer. Since few options exist for the treatment of pancreatic cancer, it is
important to identify potential targets for drug therapy. In an effort to gain more
insight into pancreatic tumonigenesis] pancreatic tumors have been analyzed at
the molecular level to detect genetic lesions. Activating mutations within the K-
ras gene have been detected in up to 90% of pancreatic carcinomas, suggesting
that activation of the Ras pathway is important in the development of pancreatic cancer (2). Experimental chemotherapeutic strategies for pancreatic cancer
patients currently include drugs which target the Ras signal transduction
pathway.

For
example, epidemiological studies have shown that prolonged use of aspirin or
other nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce the risk of
colon cancer by 40-50% (3). NSAIDs also inhibit chemically induced colon
carcinomas in animal model systems (4). Since NSAIDs are known to inhibit
cyclooxygenase. . . esters, and growth factors (5, 6). COX-2 expression has
recently been shown to be elevated in several different types of human cancer,
suggesting that the presence of COX-2 correlates with cancer development (7-
1 1). Additional studies which directly link COX-2 to carcinogenesis include
observations that human colon cancer cells expressing COX-2 acquire increased
invasiveriess (12) and that COX-2 expressed in intestinal epithelial cells inhibits
apoptosis (13). COX-2 expression in colon cancer cells has also been found to
promote angiogenesis of co-cultured endothelial cells by stimulating the production of angiogenic factors (14). Furthermore, direct genetic

evidence
linking COX-2 to colorectal tumorigenesis was
provided by a mouse model for
human familial adenomatous polyposis (FA-P), an inherited
condition leading to
  colorectal cancer; in this system, COX-2 gene
knockouts and a specific COX-2
inhibitor were found to reduce the number of intestinal
polyps formed (1 5).

The presence of oncogenic Ras has been associated with the induction of
COX-2 expression in H-ras-transformed rat intestinal and
mammary epithelial
cellsaswellasinnon-smallcelllungcancercelllines(16-18). Toour
knowledge, the association between oncogenic Ras and COX-2 expression
has
not ben explored in vivo. The high frequency of activating mutations
within the
K-ras gene in pancreatic tumors should enable us to
investigate the relationship
between oncogenic K-ras and COX-2 expression in vivo. In the present
study,
we evaluated COX-2 protein levels in primary human pancreatic
adenocarcinomas. We further examined whether COX-2 expression correlated
with K-ras mutation status in pancreatic tumors as well as in
pancreatic cancer
cell lines. In light of our data demonstrating elevated levels of COX-2
protein in
primary pancreatic tumors and cell lines, we tested the effect
of the COX
inhibitors sulindac, indomethacin and NS-398 on cell growth and
prostaglandin
E2 production in human pancreatic tumor cell lines.

Cyclooxygenase-2 (COX-2) expression is upregulated in several types of
human cancers and has also been directly linked to
carcinogenesis. To
1 5 investigate the role of COX-2 in pancreatic cancer, we
evaluated COX-2 protein
expression in primary human pancreatic adenocarcinomas (n = 23) and
matched
normal adjacent tissue (n = I 1) by immunoblot analysis. COX-2
expression was
found to be significantly elevated in the pancreatic tumor
specimens compared to
normal pancreatic tissue. To examine whether the elevated levels of
COX-2
protein observed in pancreatic tumors correlated with the
presence of oncogenic
K-ras, we determined the K-ras mutation status in a subset of the
tumors and
corresponding non-nal tissues. The presence of oncogenic K-ras did not
correlate with the level of COX-2 protein expressed in the pancreatic
adenocarcinornas analyzed. These observations were also confirmed in a
panel
of human pancreatic tumor cell lines. Furthermore, in the
pancreatic tumor cell
line expressing the highest level of COX-2 (BxPC-3), COX-2 expression
was
demonstrated to be independent of Erkl/2 Map kinase activation. The. .
. lack of
correlation between COX-2 and oncogenic K-ras expression suggests that
Ras
activation may not be sufficient to inducing COX-2 expression in
pancreatic

tumor cells and that the aberrant activation of signaling pathways other than Ras
may be required for up-regulating COX-2 expression. We also. . . report that the
COX inhibitors sulindac, indomethacin, and NS-398 inhibited cell growth in
both COX positive (BxPC-3) and COX negative (PaCa-2) pancreatic tumor
cell lines. However, suppression of cell growth by indomethacin and NS-398
was sigm icantly greater in the BxPC-3 cell line compared to. . . that COX-2 may play an important role in pancreatic
tumongenesis and therefore be a promising chemotherapeutic target for the
treatment of pancreatic cancer.

I 0
Other NSAIDs, including indomethacin and NS-398 also the growth of pancreatic tumor cell lines, as discussed hereinbelow, and can also be
used in the present method, alone, or preferably in combination with sulindac.

. . .
or infusion in dosages of about 500-4000 Mg/M2 /week for up to 7 weeks/cycle for treatment of localized or metastatic pancreatic cancer
(adenocarcinoma of the pancreas). It can also be administered in conjunction
with other anti-cancer agents, such as 5-FU. See, PDR (53rd ed., 1999) at pages
1578
The effect of sulindac or NS-398 alone and in combination with gemcitabine on the growth of pancreatic tumor cells BxPC-3 and PaCa-2 was
investigated. Treatment with the drug combinations inhibited the growth of both
cell lines to a greater extent. . . NF-KB DNA binding activity was inhibited by parthenolide treatment. These results suggest
that anti-inflammatory drugs may enhance the effectiveness of gemcitabine
against pancreatic tumors.

. . .
of a prophylactic or therapeutic dose of sulindac, an analog thereof or a combination thereof, in the acute or chronic management of
cancer, i.e., pancreatic caner, will vary with the stage of the cancer, such as the
solid tumor to be treated, the chemotherapeutic agent(s) or other anti-cancer
therapy used, and the route of administration. The dose, and perhaps the dose
frequency, will also vary according to the age, body. . .

. . .
5 chemotherapy regimen. The sulindac, in some cases, may be combined with the
same carrier or vehicle used to deliver the anti-cancer chemotherapeutic agent.

. . .
sterile powders comprising the
active ingredient which are adapted for the extemporaneous preparation of sterile
injectable or infusible solutions or dispersions, optionally encapsulated in
liposomes. In all cases, the ultimate dosage form must be

sterile, fluid and stable
under the conditions of manufacture and storage. The. . . like),
vegetable oils, non-toxic glyceryl esters, and suitable
mixtures thereof The proper fluidity can be maintained, for example, by
the
formation of liposomes, by the maintenance of the required
particle size in the
case of dispersions or by the use of surfactants. The prevention. . .
. . .
were obtained from the Indiana
University Tissue Procurement Laboratory and the Cooperative Human
Tissue
Network (CHTN) which is funded by the National Cancer
Institute. A total of
23 primary human pancreatic cancer specimens were analvzed in
this study.
. . .
within I hour of surgical
removal and subsequently stored at -80'C. Paraffin sections were
prepared from
a subset of the specimens. All tumor specimens used in this
study were
examined by a pathologist and classified as primary pancreatic
adenocarcinornas.

5. Statistical Analysis. The presence of statistically significant
elevation
of COX-2 protein between cancer specimens and corresponding
normal adjacent
tissues was determined by the nonparametric signed rank test. A two-way
analysis of variance (ANOVA) was used. . .

6. Cell Lines. The human pancreatic tumor cell lines (AsPC-1,
BxPC-3,
Capan-1, Capan-2, HPA-F-11, Hs766T, PaCa-2 and PANC-1) were obtained
from
the American Type Culture Collection (ATCC, Rockville, MD). . .
. . .
Undetectable levels of COX-2 protein were observed in each of the
normal specimens. In contrast, COX-2 protein expression in the
pancreatic
5 tumor tissues ranged from undetectable (sample #2 1) to
slight/moderate
(samples #12, 14, 20) to high levels (samples #9, 22). COX-1 protein was
observed in both pancreatic tumor and normal tissues, although
the level of
expression was variable and not consistently elevated in the
tumor specimens
(Figure 1). Similar levels of p21' and actin expression were found in
both the
tumor and corresponding normal tissues (Figure 1).
. . .
narrower range (0 3%) of COX-2
expression in the normal tissues. Both the mean and median COX-2
expression
were higher in the tumor samples, suggesting that COX-2
expression is elevated
in pancreatic adenocarcinomas compared to normal tissue. The difference
in
COX-2 expression between the pancreatic tumor and
corresponding normal
tissue was determined to be statistically significant (P = 0.004)
(Figure 2, inset).
. . .
less than 5% respectively, which

corresponds closely with visual detection in the immunoblots. According to
these criteria, 6 out of 11 (55%) tumor samples in the matched tissue sets were
COX-2 positive. Similarly, 13 out of the 23 (56%) total tumor specimens
analyzed were COX-2 positive; in contrast, all the normal tissue samples (n
I 1) were COX-2 negative.

h-nmunohistochemical staining of the pancreatic tumor specimens
demonstrated that COX-2 expression was localized to the carcinoma cells and
was not detectable in the stromal compartment of the tumors (Figure 3).

Example 2
COX-2 expression and K-ras mutation in pancreatic tumors and cell lines
To determine if COX-2 expression levels correlated with the K-ras mutation status of the tumors, genomic DNA was isolated from a subset of the
tissue specimens and screened for the presence of K-ras mutations at codon. . .
.
the
normal tissues analyzed were wild-type at codon 12 (GGT = Gly) and codon 13
(GGC = Gly). Of the 13 pancreatic cancer specimens analyzed, one specimen
had a mutation at codon 13 whereas IO samples were mutated at codon 12,
corresponding to a K-ras. . . extent of COX-2 protein expression. For example, some samples expressed high levels of COX-2 protein
and possessed a mutation in K-ras (i.e., tumor samples #9, 16 and 22); however,
other samples which had mutated K-ras expressed little or no COX-2 protein
(i.e., tumor samples #3, 17, 18, 19, and 21).
.
with known K-ras mutation status (25, 26). Both the frequency and variability in the quantity of COX-2 expressed in the pancreatic tumor cell lines
reflected our findings in the primary pancreatic adenocarcinomas. Of the eight
human pancreatic tumor cell lines analyzed, only three of the seven cell lines
expressing oncogenic K-ras exhibited detectable levels of COX-2 protein
(Capan-1, Capan-2 and. . . (Figure 4B). Taken
together, our results suggest that activation of the Ras pathway is not sufficient
for mediating COX-2 uprecrulation in pancreatic tumor cells. We also compared
the level of COX-2 expression in three hamster pancreatic cell lines, The
D27/K-ras and B 12/13 transformed cell. . . parental line (Figure 4Q. These results confirm our conclusion that
Ras activation alone is not sufficient for upregulating COX-2 expression in
pancreatic cancer cells and suggest that additional events which occur following
exposure to chemical carcinogens may be required.

To examine whether COX-2 expression could be induced in the human

pancreatic cancer cell lines, four cell lines were serum-starved and subsequently treated with IO% FCS for various time periods (F1 crure 4D). In. . . . is activated (unpublished observations), again demonstrating that Erk 1/2 activation is not sufficient for inducing COX-2 expression in the COX negative pancreatic tumor cells. We observed similar results upon treating the cell lines with the tumor promoter, PMA (unpublished observations).

Example 3
Treatment of pancreatic tumor cell lines with cyclooxygenase inhibitors
The COX positive human pancreatic tumor cell lines, BxPC-3, and the COX negative cell line, PaCa-2, were treated with the COX inhibitors sulindac, indomethacin, or NS Sulindac and. . . was measured after three days of treatment (Figure 5). All three inhibitors were found to suppress cell growth in both pancreatic tumor cell lines in a dose-dependent manner. However, indomethacin and NS-398 were found to inhibit cell growth to a greater extent in the. . .

To evaluate the functional activity of COX-2 in the human pancreatic tumor cell lines, prostaglandin E2 (PGE,) production was measured by enzymeimmunoassay (Figure 6A). PGE2 production was elevated in the BxPC-3, Capan-1, Capan-2. . .

These data demonstrate that the combination of sulindac and gemcitabine is more effective than either compound alone in pancreatic tumor cells.

. . . as well as inflammatory agents (5, 6, 29). Recent studies have shown that COX-2 expression is upregulated in a variety of human cancers, including colon, lung, gastric, pancreatic and esophageal (7-1 1). In the present study, we report that elevated levels of COX-2 protein are expressed in human pancreatic tumors compared to barely detectable levels in the matched non-nal pancreatic tissue, suggesting that increased expression of COX-2 protein correlates with pancreatic tunionigenesis. Our results confirm a recent report demonstrating upregulation of COX-2 RNA and protein in pancreatic tumors and localization of COX-2 in malignant epithelial cells (I 1). An earlier study demonstrated that the expression of group 11 phospholipase A2,. . . phospholipids, was higher in pancreatic ductal adenocarcinomas compared to normal pancreatic tissue (30). In addition, the development of N-nitrosobis(2-oxopropyl)amine (BOP)-initiated pancreatic tumors in hamsters was inhibited bv the administration of two prostaglandin synthesis inhibitors, phenylbutazone and indomethacin (3 1). Together with our observations in. . . that increased prostaglandin production due to the increased expression of COX-2 may be an important event in the

multi-step
progression towards pancreatic tumor formation.

. . .

as well as prostaglandin E2 were detected in Ras-transformed mammary epithelial cells (C57/MG) cells (I 7). In human non-small cell lung cancer
(NSCLQ cell lines expressing oncogenic K-Ras, increased PGE2 production was
5 mediated by constitutively high expression of cytosolic, phospholipase A, and
COX-2 compared. . . the expression of detectable levels of
COX-2 protein. A possible explanation for the lack of COX-2 expression in a
subset of the tumors with oncogenic Ras is that Erkl/2
activity may be down-
regulated in pancreatic carcinomas (26). Moreover, even in the two pancreatic
tumor samples which did show elevated levels of activated
Erkl/2 (samples #4
and 21, data not shown), only low levels of COX-2. . . in the present study, suggesting that Erkl/2 activation alone is not sufficient for inducing
COX-2 expression. These findings suggest that within the tumor environment,
the presence of oncogenic K-ras does not directly result in increased COX-2
expression in pancreatic cancer.

Similar conclusions were also reached upon analysis of pancreatic cancer
cell lines, which were examined since they represent a homogenous population
of cells as opposed to primary tumor tissue which is
heterogenous. Despite
activating K-ras mutations in seven out of the eight lines, only three of the lines
with mutated. . . of COX-2
expression. Activation of other signaling pathways in addition to Ras may
cooperate to determine the extent of COX-2 expression in cancer
cells. Such
pathways may include the p38 mitogen-activated protein kinase which has been
reported to regulate the induction of COX-2 in lipopolysaccharide-
treated. . . the cell type as well as the stimulus. Further experiments will
be required to delineate which signaling pathways are function in pancreatic
tumor cells.

. . .

expressing cell lines. These
data suggest that the COX inhibitors exert their inhibitory effects by both
COX/PGE,-dependent and -independent pathways in pancreatic tumor
cell lines.

The detection of elevated levels of COX-2 in a variety of human cancers
combined with the chemopreventative effect of NSAIDs in colon cancer
I 0 demonstrate that COX-2 is an important participant in carcinogenesis. The
reported biological consequences of COX-2 upregulation include inhibition of
apoptosis (13), increased metastatic potential (12) and promotion of

anglogenesis
(14). These events may contribute to cell transformation and tumor progression.

COX-2 expression was noticeably elevated in 55% of the patient pancreatic
tumor samples analyzed, identifying COX-2 as a new target for chemotherapy.

These results demonstratincy the ability of COX inhibitors to inhibit pancreatic
tumor cell growth and PGE, production in vitro indicate that NSAIDs may be
effective in the treatment of pancreatic cancer patients, for whom few treatment
options currently exist. COX-2 expression is also useful as a prognostic or
diagnostic tool.

1. Landis et al., CA Cancer J. Clin., 49, 6-29 (1998).

3. Thun, M.J., Cancer Metastasis Rev., ia, 269-77 (1994).

4. Giardiello et al., Eur. J. Cancer, 31A, 1071-6 (1995).

8. Ristimaki et al., Cancer Res., 52, 1276-80 (1997).

9. Zimmermann et al., Cancer Res., 59-, 198-204 (1999).

10. Wolff et al., Cancer Res., 5.-a, 4997-5001 (1998).

1 1. Tucker et al., Cancer Res., 52, 987-90 (1999).

25. Berrozpe et al., Trit. J. Cancer, 5S, 185-91 (1994).

35. Elder et al., Clin, Cancer Res-, a, 1679-83 (1997).

36. Piazza et al., Cancer Res., 52, 2909-15 (1997).

TABLE 1. Analysis of Patient Samples

Tissue Sample'	Tissue Type	% COX-2 b	% Cancer'	K-raE
I	pancreatic adenocarcinorna	7.0	10	WT
2	pancreatic adenocarcinorna	2.0	95	
3	pancreatic adenocarcinoma	0.2	15	GGC to CG,
4	pancreatic adenocarcinorna	3.6. . .	N nornial	0.1 -
12	pancreatic adenocarcinorna	I	15	
14	pancreatic adenocarcinorria	31	ND	

Tissue Sample a	Tissue Type	% COX-2 b	% Cancer'	K-ras
1 5	pancreatic adenocarcinonia	7.8	25	GGT to
15N	normal	4.3 - I		
1 6	pancreatic adenocarcinoma	66	35	GGT to
16N	non-nal. . .			

c The percent cancer was determined by visualization following hematoxylin/eosin staining
of slides prepared from paraffin sections.

CLMEN I . A method of reducing the viability of pancreatic cancer cells comprising
contacting the cancer cells with an effective amount of an NSAID.

2 A method of increasing the susceptibility of mammalian pancreatic
cancer cells to a chemotherapeutic agent comprising contacting the cells with an

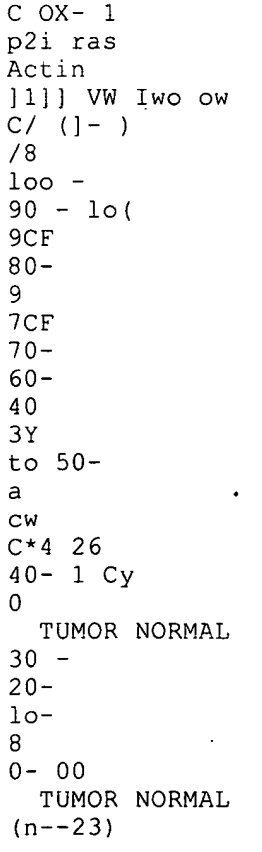
effective sensitizing amount of an NSAID.

4 The method of claim I or 2 wherein the mammalian cancer cells are human cancer cells.

5 The method of claim 3 wherein the sulindac or the analog thereof is administered to a human cancer patient.

6 The method of claim 5 wherein the cancer patient is undergoing treatment with a chemotherapeutic a2ent.

9 A method of evaluating the ability of sulindac or an analog thereof that is a COX-2 inhibitor to sensitize pancreatic cancer cells to a chemotherapeutic agent comprising:
(a) isolating a first portion of pancreatic cancer cells from a human pancreatic cancer patient;
(b) measuring their viability;
(c) administering sulindac or the analog thereof to said patient;
(d) isolating a second portion of pancreatic cancer cells from said patient;
(e) measuring the viability of the second portion of pancreatic cancer cells; and
(f) comparing the viability measured in step (e) with the viability measured in step (b); wherein reduced viability in step (e) indicates.



y1wMian = 5.2% median = 02%
nwan = 15.2 +/- 24.9% mcan 0.83 +/- 1.3%
v2mge = 0 - 93% map 0. . . Sulindac IndometIL NS-398
% inhibition: 0 07 90 F957 98 759 86
/8
Effect of Sulindac + Gemcitabine on the growth of the
pancreatic tumor cell line, BxPC-3 (day 3)
125 -
100 I Gem alone
75 -
1,100+ e
50 - T
em
sul, 500 + Gem
0 5 10 15 20. . . and Technology Institute, Inc.
Marshall, Mark Steven
Sweeney, Christopher J.
Yip-Schneider, Michele T.
Crowell, Pamela L.
10<120> Use of NSAIDs for the treatment of pancreatic cancer
<130> 740.018WO1
<150> US 60/165,543
15<151> 1999 15
<160> 2
<170> FastSEQ for Windows Version 4.0
<210> 1
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<212> DNA
<213> Homo sapiens
<400> 1
atgactgaat ataaacttgt 20
<210> 2
30<211>. . . search (name of data base and, where practical, search
terms used)
EPO-Internal, WPI Data, PAJ,, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS,
CANCERLIT
C. DOCUMENTS CONSIDERED TO BE RELEVANT
Category Citation of document, with indication, where appropriate, of
the relevant passages Relevant to claim No.
PqX SWEENEY J. ET AL.: INHIBITION OF CELL 1-11
GROWTH IN PANCREATIC TUMOR CELLS BY
ANTI-INFLAMMATORA DRUGS11
PROCEEDINGS OF THE AMERICAN ASSOCIATION
FOR CANCER RESEARCH,
vol. 41, March 2000 (2000-03),, page 527
XPOO2164391
USA
ABSTRACT #3358
abstract
Further documents are listed in the continuation of box C. Patent family
members. . . passages Relevant to claim NO.
PqX MARSHALL M.S. ET AL.: SUPPRESSION OF 1-11
PANCREATIC DUCTAL ADENOCARCINOMA GROWTH BY
SULINDACH
PROCEEDINGS OF THE AMERICAN ASSOCIATION
FOR CANCER RESEARCH,
vol. 41, March 2000 (2000-03), page 526
XPOO2164392
USA
ABSTRACT #3349
abstract
P9X T.YIP-SCHNEIDER M. ET AL.: COX-2 1-11
EXPRESSION IN HAMAN PANCREATIC
ADENOCARCINOMAS11
CARCINOGENESIS,

vol. 21, no. 2,. . . XPOO0984815
the whole document
X MOLINA M, ET AL.: INCREASED COX-2 1-11
EXPRESSION IN HUMAN PANCREATIC CARCINOMAS
AND CELL LINES: GROWTH INHIBITION NY
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS11
CANCER RESEARCH,
vol. 59, no. 17, September 1999 (1999-09),
pages 4356-4362, XPOO0984712
the whole document
X WO 99 49859 A (THE ARIZONA BOARD OF 1-698
REGENTS). . .

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---Logging off of STN---

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Executing the logoff script...

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
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 NEWS EXPRESS  DECEMBER 02 CURRENT VERSION FOR WINDOWS IS V8.01,
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=> s microspher?
L1       15203 MICROSPHER?

=> s l1/ti
L2         343 (MICROSPHER?/TI)

=> s l1/ab
L3         990 (MICROSPHER?/AB)

=> s l2 or l3
L4        1026 L2 OR L3
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=> s polyanhydride
          1149 POLYANHYDRIDE
          5384 POLYANHYDRIDES
L5        6164 POLYANHYDRIDE
                (POLYANHYDRIDE OR POLYANHYDRIDES)

=> s sulindac
L6        2826 SULINDAC

=> s l6 and l4
L7          16 L6 AND L4

=> s l7 and l5
L8           3 L7 AND L5

=> d ibib 1-3

L8     ANSWER 1 OF 3     PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        2005081825 PCTFULL  ED 20050914  EW 200536
TITLE (ENGLISH):         ABUSE RESISTANT OPIOID TRANSDERMAL DELIVERY DEVICE
                         CONTAINING OPIOID ANTAGONIST MICROSPHERES
TITLE (FRENCH):          DISPOSITIF DE DISTRIBUTION TRANSDERMIQUE D'OPIOIDES
                         EMPECHANT UNE UTILISATION ABUSIVE ET CONTENANT DES
                         MICROSPHERES D'ANTAGONISTES D'OPIOIDES
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                         LONG, Kevin, 3 Hidden Hill Road, Oak Ridge, NJ 07438,
                         US [US, US];
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                         [US, US], for US only;
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                         US [US, US], for US only;
                         TAVARES, Lino, 86 South Glen Road, Kinnelon, NJ 07405,
                         US [US, US], for US only;
                         LONG, Kevin, 3 Hidden Hill Road, Oak Ridge, NJ 07438,
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                         MASKIEWICZ, Richard, 88 Saunders Lane, Richfield, CT
                         06877, US [US, US], for US only;
                         SHAMEEM, Mohammed, 4 Surim Court, Nanuet, NY 10954, US
                         [US, US], for US only
AGENT:                   DAVIDSON, Clifford, M.$, Davidson, Davidson & Kappel,
                         LLC, 485 Seventh Avenue, 14th Floor, New York, NY
                         10018$, US
LANGUAGE OF FILING:      English
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DOCUMENT TYPE:           Patent
PATENT INFORMATION:
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APPLICATION INFO.: WO 2005-US4741 A 20050215
PRIORITY INFO.: US 2004-60/547,196 20040223

L8 ANSWER 2 OF 3 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 2004052339 PCTFULL ED 20040630 EW 200426
TITLE (ENGLISH): PH TRIGGERED TARGETED CONTROLLED RELEASE SYSTEMS
TITLE (FRENCH): SYSTEMES DE LIBERATION CONTROLEE CIBLEE A DECLENCHEMENT FONCTION DU PH
INVENTOR(S): SHEFER, Adi, 14 Jason Drive, East Brunswick, NJ 08816, US;
SHEFER, Samuel, David, 14 Jason Drive, East Brunswick, NJ 08816, US
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AGENT: DUNN, McKay, Diane$, Mathews, Collins, Shepherd & McKay, P.A., 100 Thanet Circle, Suite 306, Priceton, NJ 08540$, US
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
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WO 2004052339	A1	20040624

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APPLICATION INFO.: WO 2003-US26142 A 20030821
PRIORITY INFO.: US 2002-10/315,801 20021209

L8 ANSWER 3 OF 3 PCTFULL COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER: 1996040090 PCTFULL ED 20020514
TITLE (ENGLISH): METHOD FOR REDUCING OR PREVENTING POST-SURGICAL ADHESION FORMATION USING 5-LIPOXYGENASE INHIBITORS
TITLE (FRENCH): PROCEDE POUR LA REDUCTION OU LA PREVENTION DE LA FORMATION D'ADHERENCES POST-CHIRURGICALES A L'AIDE D'INHIBITEURS DE 5-LIPOXYDASE
INVENTOR(S): RODGERS, Kathleen, Elizabeth;
diZEREGA, Gere, Stodder
PATENT ASSIGNEE(S): UNIVERSITY OF SOUTHERN CALIFORNIA
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

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WO 9640090	A1	19961219

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W: AU CA JP AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL
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